



Catalysis of the Knoevenagel reaction by γ -aminopropylsilica

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Abstract

The Knoevenagel reaction can be catalysed by γ -aminopropylsilica. Reactions are rapid and essentially quantitative with small amounts of catalyst. A range of aldehydes and ketones can be reacted successfully, the only exceptions being very bulky ketones. The reaction is very dependent on the efficient removal of water, which leads to faster reaction rates and to much higher conversions. The choice of solvent is also extremely important, with nonpolar solvents such as cyclohexane being optimal. Less polar, higher boiling solvents are significantly less effective, even at much higher reaction temperatures. Catalyst poisoning is slow and appears to be due to amide formation on the surface.

Keywords: Green chemistry; Silica; Base catalysis; Solvent effects; Knoevenagel

1. Introduction

The Knoevenagel reaction is one of the most important C–C-bond-forming reactions available to the synthetic chemist [1]. It is also potentially one of the most environmentally friendly, having water as its sole coproduct. The major drawback to the use of the Knoevenagel reaction in environmental terms has been the difficulty of finding suitable catalysts for some of the more demanding reaction partners. For example, organic bases and often base–acid pairs such as piperidine/acetic acid are typically used for the more straightforward reactions, whereas the more demanding variations (i.e. those involving deactivated aromatic ketones) rarely give respectable yields. The use of heterogeneous bases as catalysts for this reaction has been reported before

[2–7], but the amount of catalyst used has often been prohibitive (e.g. Ref. [3] requires ca 1 kg catalyst per mole) and very few reports have mentioned any but the most straightforward reactions, such as that between benzaldehyde and malononitrile [4–7]. We now wish to report the results of our investigations into the catalysis of the Knoevenagel condensation of aldehydes and ketones using simple aminopropyl-substituted silica as catalyst. The procedure results in high yields, uses small quantities of catalyst, and is effective even for deactivated ketones.

2. Experimental

2.1. γ -Aminopropylsilica 1

Silica gel (Kieselgel 100, Merck) was dried in a fan oven at 300°C overnight, and allowed to cool. A typical preparation was as follows:

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10 g of the thermally treated silica was added to toluene (50 ml). To this was added 30 mmol of 3-aminopropyl(trimethoxy)silane (ABCR, Karlsruhe, 98%), and the mixture refluxed for 18 h with mechanical stirring. The resulting slurry was cooled, and the modified silica was filtered, washed with toluene, acetone, water, and finally twice with acetone (each washing 50 ml). After allowing to dry at room temperature, the aminopropylsilica was dried in an oven at 100°C overnight.

2.2. Catalyst characterization

1 was characterised by Diffuse Reflectance FTIR (Perkin-Elmer 1720 Infra-red Spectrometer) as a mixture with KBr. The spectra were recorded under vacuum (650 N m^{-2}) and at 130°C in order to remove water from the sample. ^{13}C -CP-MAS NMR spectra were recorded on a Bruker MSL 300 MHz CP-MAS NMR. The loading of aminopropyl groups was determined by Elemental Analysis, and by titration (addition of catalyst to dilute HCl, followed by filtration and back titration of the solution with dilute NaOH). Porosity measurements were carried out using a Quantasorb Porosimeter and Specific Surface Area was calculated using the BET method.

2.3. Reactions

A typical Knoevenagel reaction was carried out as follows: **1** (0.25 g) was added to 25 ml of solvent, and the mixture heated to reflux (with a Dean and Stark trap for the removal of water in some cases). 20 mmol of the two reaction partners were then added, along with 0.30 g dodecane as GC internal standard. GC samples were taken at intervals via a septum and analysed on a Hewlett Packard HP6890 GC. Confirmation of product structure was carried out using a Finnegan Matt Magnum GCMS instrument. Products were isolated by column chromatography and their structure was confirmed by 270 MHz ^1H NMR. The isolated products were used to calibrate the GC internal standard.

3. Results and discussion

3.1. Nature of the catalyst

Infra-red and NMR spectra showed the presence of aminopropyl groups (2880, 2935, 1602 cm^{-1} ; 45.8, 28.3, 11.5 ppm, respectively). No peak was seen which could be assigned to residual MeO groups either on the silane or on the silica support, indicating that the majority of the SiOMe groups have been replaced by either SiOSi or SiOH groups. Elemental analysis is in agreement with this finding, in that the C:N ratio was found to be 3.4. Surface loading was 1.0 mmol g^{-1} based on %N. As a second analytical method, the catalyst was stirred for varying amounts of time in contact with a dilute (0.01 M) solution of HCl, filtered and the acid solution back-titrated with NaOH. Titration after 5 min, 1 h, 2 h and 24 h contact times all led to a loading of basic sites of 0.95–1.03 mmol g^{-1} .

Surface area analysis indicated a specific surface area (SSA) of $254 \text{ m}^2/\text{g}$. Pore size distribution was broad and centred on 8 nm, and was essentially identical to that of the parent silica.

3.2. Reaction studies

It has been previously reported that **1** is capable of catalysing the Knoevenagel reaction [3]. The work described in this reference relates to a column reactor, in which the reactants are passed over a column packed with catalyst. While this is a convenient method in many respects, and gives good yields of product in a range of reactions, it requires large amounts of catalyst. Apart from this paper, there is, as far as we are aware, no study where the catalyst is used in more demanding reactions than the very simple condensation of aldehydes and malononitrile or ethyl cyanoacetate. We have studied the Knoevenagel reaction using **1** under more typical stirred reactor conditions in order to define the activity of the catalysts. In order to carry out this study we have investigated a range of operational parameters, including reactants, reaction temperature, solvent, and catalyst poisoning.

Table 1

Reaction of carbonyl compounds with ethyl cyanoacetate in cyclohexane with **1** as catalyst; except where stated, reactions were carried out with water removal

$\begin{array}{c} \text{R} \\ \\ \text{R}-\text{C}=\text{O} \end{array} + \begin{array}{c} \text{CO}_2\text{Et} \\ \\ \text{CN} \end{array} \longrightarrow \begin{array}{c} \text{R} \\ \\ \text{R}-\text{C}=\text{C}-\text{CO}_2\text{Et} \\ \\ \text{CN} \end{array} + \text{H}_2\text{O}$						
R	R'	Temp. (°C)	Time (h)	Yield ^a (%)	TON ^b	
Ph	H	25	4	99 ^c		
<i>n</i> -C ₅ H ₁₁	H	25	7	97 ^c		
<i>n</i> -C ₇ H ₁₅	H	25	8	98 ^c		
	<i>c</i> -C ₅ H ₁₀	82	1	98	650	
Et	Et	82	2	97	265	
Et	Et	82	4	65 ^c		
<i>n</i> -C ₄ H ₁₀	Me	82	4	98		
<i>t</i> -C ₄ H ₁₀	Me	82	24	22		
Me	Ph	82	24	68	250	
Ph	Ph	82	72	8		

^a GC yields with *n*-dodecane as internal standard. Isolated yields are 5–10% lower.

^b Number of moles product per mole of NH₂ groups.

^c Reaction carried out without removal of water.

3.2.1. Scope of reaction

It was found that aldehydes and most types of ketones will react successfully under catalysis by **1** (Table 1). Only the sterically hindered ketones benzophenone and methyl-*t*-butylketone (MTBK) fail to give good yields. With the exception of these two ketones the reaction proceeds smoothly to the unsaturated product, with no evidence for the intermediate alcohol, and no other side reactions, such as Michael reactions occurring. Aliphatic aldehydes cyclotrimerise extremely rapidly, but the trimer reacts normally. In the reaction of benzophenone and MTBK the intermediate alcohol is seen in the reaction mixture if the GC injector temperature is lowered to <150°C, but steric reasons hinder the second step, and the alcohol decomposes preferentially to reactants.

3.2.2. Role of water

A particularly important point arises regarding the removal of water from the system. In reactions where water was continuously removed (by a Dean and Stark trap) the rate, conversion and yield all increase significantly. This has not been

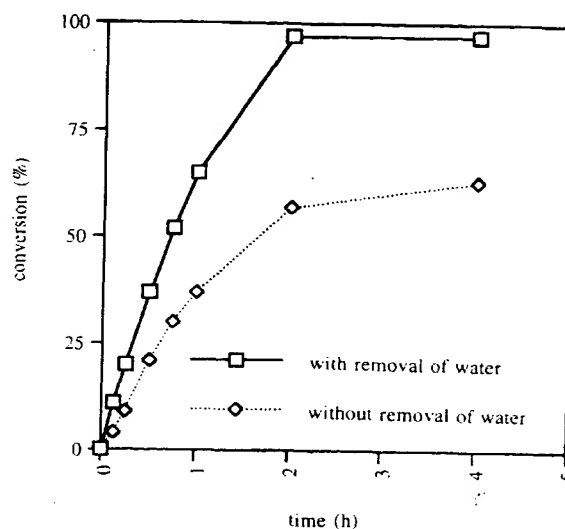


Fig. 1. Progress of reaction between ethyl cyanoacetate and 3-pentanone. Effect of water.

investigated for aldehydes, whose reactivity is already high enough that the reactions take place at room temperature. However, the effect of water removal can be seen from the representative example of 3-pentanone and ethyl cyanoacetate, in both Table 1 and Fig. 1. This effect is general, over the range of ketones studied, and increases the conversion from, typically, 50–70% to almost quantitative. The increase in rate shown in Fig. 1 is also typical, and, while not enormous, is certainly significant.

Turnover numbers were measured for a few reactions. These were measured by carrying out a normal reaction as described with the batchwise addition of more reactants until no more conversion was achieved. Similar results were achieved by decantation of most of the product solution, followed by addition of fresh reaction mixture. Filtration of the catalyst followed by drying and reuse resulted in significant deactivation and turnover numbers much lower than those achieved when the catalyst was not isolated. The reasons for this deactivation on exposure to the atmosphere are not known. The catalysts are stable at room temperature in glass jars for several months without protection against light, air or moisture.

Similarly, the possibility of leaching and homogeneous catalysis was excluded by removing the catalyst from a reaction mixture after ca. 30% conversion. No further conversion was seen after this point.

3.2.3. Solvent effects

The results shown in Table 1 were all achieved in cyclohexane. The sensitivity of a heterogeneously catalysed reaction to solvent can often be of great importance [8,9], and thus several solvents were investigated. The solvents studied were chosen to cover a range of temperatures and solvent parameters, and for their ability to allow continuous removal of water from the reaction system. The results are shown in Fig. 2. As can be seen, there is a remarkable solvent dependency. It is clear that the reaction rate correlates

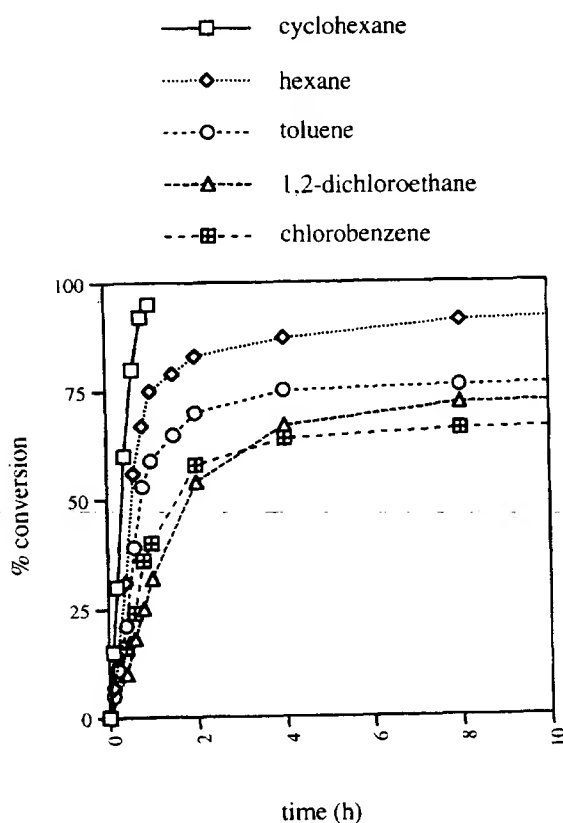


Fig. 2. Solvent effects on the reaction between 3-pentanone and ethyl cyanoacetate.

Table 2

Selected solvatochromic parameters for the solvents studied

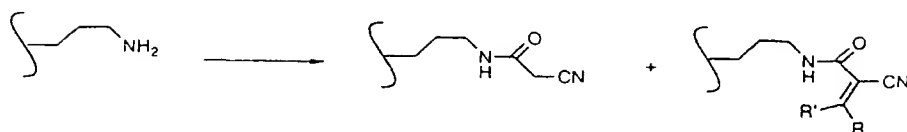
Solvent	bp (°C)	β	α	π^*	E_T^N
Hexane	68	0.00	0.00	-0.08	0.009
Cyclohexane	80	0.00	0.00	0.00	0.006
Toluene	110	0.55	0.00	0.54	0.099
1,2-Dichloroethane	83	0.00	0.00	0.81	0.327
Chlorobenzene	131	0.07	0.00	0.71	0.188

with both polarisability (π^*) [10] and polarity E_T^N [11], indicating that these factors are of prime importance, masking even the expected effect of temperature (Table 2). No correlation with other solvent parameters is obvious, although the range of solvents studied is still fairly limited – the effect of water removal precludes a completely free choice to be made. The exact reasons for the ability of low polarity solvents to support the reaction to a far greater extent than the more polar/polarisable ones are not yet clear, although a partitioning of reactants onto the polar catalyst surface is one possible explanation. Work is continuing on this aspect of the reaction, and results will be presented in due course.

3.2.4. Catalyst poisoning

After the catalyst had lost activity, it was isolated by filtration and washed with ethyl acetate several times. The catalyst was then dried at 30°C under vacuum (1 Torr) for 18 h and analysed. DRIFT infra-red indicated new intense bands (1661 cm^{-1} and 1545 cm^{-1} , and two peaks of medium intensity at 2261 cm^{-1} and 2206 cm^{-1}). These bands remained after several washes with hot ethanol. This is consistent with the formation of amide groups on the surface via the reaction of the amine group and the ester groups of the starting material and the product (Scheme 1)

In order to confirm this, and to refute other possible poisoning reactions, we reacted the catalyst with both reactants separately. Other possible reactions of silica bound primary amino groups include imine formation. This is a rapid reaction with aldehydes, and occurs readily with ketones [12]. The catalyst was heated with the car-



Scheme 1. Postulated poisoning mechanism.

bonyl component in cyclohexane, and the catalyst reisolated and washed. Infra-red analysis showed formation of imines, but the IR bands did not correspond with those seen for the poisoned catalyst (one sharp band at 1630 cm^{-1} to 1645 cm^{-1} depending on the nature of the carbonyl compound used). The rapidity of the formation of the imine, and its lack of identity with the poisoning species, indicates that it is not involved in the poisoning, but could potentially be an intermediate in the reaction. Reaction of ethyl cyanoacetate with the catalyst in cyclohexane under re-

flux resulted in a spectrum displaying the same peaks as the poisoned catalyst (Fig. 3). The CN-str. band of ethyl cyanoacetate and products are 2231 cm^{-1} and $2226\text{--}2233\text{ cm}^{-1}$, respectively, indicating that the infra-red bands are not from physisorbed esters, but are more likely due to chemisorbed (via amide) species. The bands at 1661 cm^{-1} and 1545 cm^{-1} are consistent with amides attached to silica [13]. Thus, the poisoning of the catalyst can be ascribed to a slow reaction of the ester groups present in the reactant/product with the active centres of the catalyst.

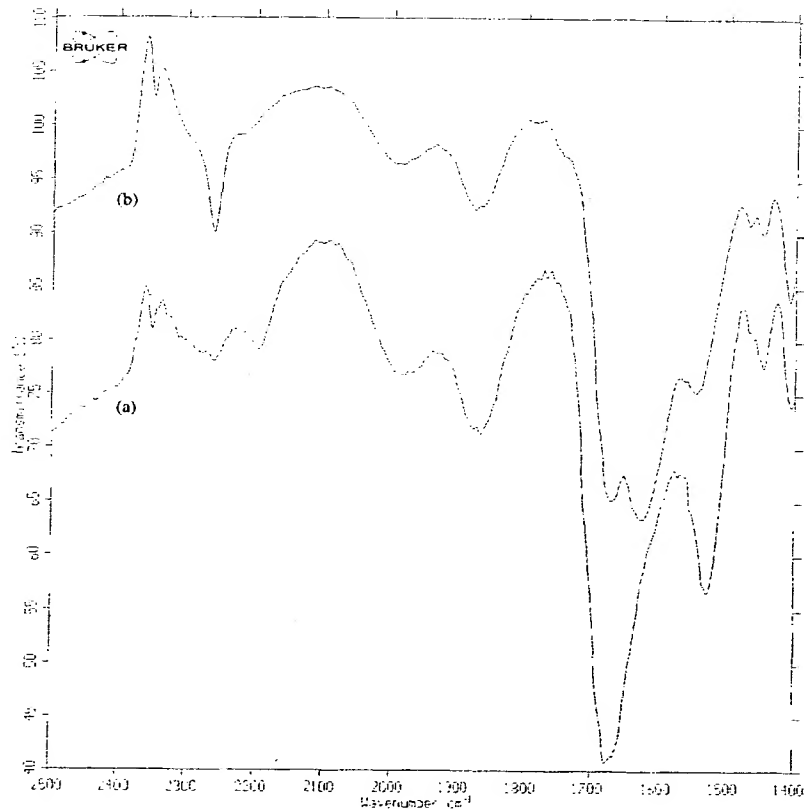


Fig. 3. Comparison of DRIFT IR spectra of poisoned catalyst (a) and fresh catalyst after reaction with ethyl cyanoacetate (b).

4. Conclusions

γ -Aminopropylsilica is an effective catalyst for the Knoevenagel condensation of a wide range of carbonyl compounds. The reaction displays a pronounced solvent effect, and is much more successful when water is continuously removed. Best activity is seen in nonpolar systems. Deactivation appears to be due to the slow formation of surface bound amides. Future work will concentrate on the origin of the solvent effect, and the use of alternative basic groups which may be less prone to deactivation.

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